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Fetoscopic versus Open Repair for Spina Bifida Aperta: A Systematic Review of Outcomes

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Key Words
Spina bifida · Myelomeningocele · Fetal surgery · Fetoscopy · Open fetal surgery · Systematic review

Abstract
Objective: To compare outcomes of fetoscopic spina bifida aperta repair (FSBAR) with the results of the open approach (OSBAR) as in the Management Of Myelomeningocele Study (MOMS). ***Methods:*** This was a systematic comparison of reports on FSBAR with data from the MOMS (n = 78). Inclusion criteria were studies of spina bifida aperta patients who underwent FSBAR and were followed for ≥12 months. Primary outcome was perinatal mortality. Secondary outcomes included operative, maternal, fetal, neonatal and infant outcomes. ***Results:*** Out of 16 reports, we included 5 from 2 centers. Due to bias and heterogeneity, analysis was restricted to two overlapping case series (n = 51 and 71). In those, FSBAR was technically different from OSBAR, had comparable perinatal mortality (7.8 vs. 2.6%, p = 0.212) and shunt rate at 12 months (45 vs. 40%, p = 0.619), longer operation time (223 vs. 105 min, p < 0.001), higher preterm prelabor membrane rupture rate (84 vs. 46%, p < 0.001), earlier gestational age at birth (32.9 vs. 34.1 weeks, p = 0.03), higher postnatal reoperation rate (28 vs. 2.56%, p < 0.001) and absence of uterine thinning or dehiscence (0 vs. 36%, p < 0.001). Functional outcomes were not available. ***Conclusion:*** FSBAR utilizes a different neurosurgical technique, takes longer to complete, induces more prematurity, requires additional postnatal procedures, yet has a comparable shunt rate and is not associated with uterine thinning or dehiscence. Long-term functional data are awaited.

This study was presented at the First Workshop of the European Club for Fetal Surgery, Sils, January 2015, and the 34th Annual Meeting of the International Fetal Medicine and Surgery Society, Hersonissos, June 2015.

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Background

Spina bifida is the most common neural tube defect occurring in 4.9/10,000 births from (EUROCAT Registry from 2008 to 2012). Theoretically, there are around 2,600 cases in the EU – 28 per year [1]. In its open ('aperta') form, spina bifida should be diagnosed prenatally and presents as a progressive disease [2, 3]. In utero deterioration is usually explained by the 'two-hit' pathogenesis [4, 5]. Firstly, there is the failed closure of the neural tube by the 6th week of gestation. Subsequently, from the 16th week onwards, there is secondary damage to the exposed spinal cord and nerves due to direct trauma and neurotoxic agents in the amniotic fluid, as well as to the brain, evidenced by the development of ventriculomegaly and Chiari II malformation (CM) [6–9]. The latter is due to cerebral spinal fluid leakage at the level of the defect, leading to a 'suction gradient' [10].

Spina bifida aperta (SBA) is a nonlethal yet chronic disease carrying a significant morbidity; its severity essentially depends on the level of the defect [11, 12]. Children may have difficulties in ambulation due to sensorimotor lower limb deficits, as well as bladder, bowel and sexual dysfunction [11]. SBA may lead to progressive complications after birth, mainly due to CM, severe hydrocephalus requiring shunting and leading to cognitive impairments namely learning disabilities, and sensorimotor deficits [11]. Tethered spinal cord syndrome is mainly a complication at the site of the repair, which can cause progressive deficits and require untethering [11, 13]. CM remains the leading cause of death within the first 5 years of life due to hindbrain dysfunction developing in 17% of SBA cases [14].

The randomized Management Of Myelomeningocele Study (MOMS) has caused a paradigm shift in the perinatal management of SBA when the diagnosis is made at the latest in the second trimester: MOMS provided level I evidence that in utero SBA repair (SBAR), as opposed to postnatal repair, reduces the need for ventriculoperitoneal shunting and improves motor outcomes at 30 months [15]. This technique consists of a layered repair which is done by maternal laparotomy and hysterotomy (open access; OSBAR). OSBAR is a highly invasive operation carrying risks for both the mother and the fetus [15]. As a consequence, fetoscopic techniques for SBAR (FSBAR) were conceived in order to minimize invasiveness, decreasing maternal morbidity while maintaining the improved infant outcomes [16]. Clinical SBAR was first performed by fetoscopy in the USA. However, it was quickly abandoned because of technical limitations and serious complications in a small case series [16–18]. In Europe, the technique was pioneered by Kohl et al. [19], initially in Bonn (Germany). Over the years, these surgeons accumulated a large surgical experience, which they published in different reports [20, 21]. Neonatal outcomes, as independently assessed by a Dutch team [22], are available for a limited number of their patients.

Following the publication of the MOMS trial and intensive training, our team decided to offer OSBAR [23, 24]. As we still have an interest in fetoscopic surgery, we aimed to systematically review the results of FSBAR [24, 25]. As a point of reference we chose the results obtained in the MOMS trial, which should be currently considered as the gold standard for treatment [15].

Data Sources

Search Strategy

We performed a systematic review in PubMed, Medline (NCBI databases), ISI web of science, EMBASE, Scopus and the Directory of Open Access Journals. In addition, we included a search of the gray literature (Google Scholar), personal communications as well as a hand search of high-impact journals in the field using the reference lists of all identified articles. The latest search update included foreign language articles and papers up to September 2015. The terms (free text and MeSH) used for the search were 'spinal dysraphism', 'spina bifida (cystica)' or 'myelomeningocele' combined with 'f(o)etoscopy' or 'f(o)etal therapy' as well as the names of authors leading a program of fetal SBAR. This systematic review was registered in the PROSPERO registry (CRD 42015017172; April 6, 2015).

Two authors (L.J. and A.C.E.) reviewed the material. To be eligible for inclusion, studies had to report on singleton fetuses with an isolated SBA who underwent fetoscopic repair and were followed for at least 12 months. In order to avoid publication bias, all relevant studies, conference presentations and interim evaluations, regardless of publication status, were included. The full texts of eligible studies were reviewed. A standardized form was used to extract data from the included studies. The primary outcome was perinatal mortality, i.e. number of fetal and postnatal (within 28 days of life) deaths. Secondary outcomes were operative, maternal, fetal, neonatal and infant outcomes. Other characteristics included whether there was potential overlap with previous reports and whether the fetoscopic program was still active (hence additional outcomes should be available and authors should be contacted). The reports were categorized as either studies on early experience (≤30 cases), a cutoff proposed by Kohl [26, 27], or beyond that point (referred to as 'later' experience). Cases reported as abstracts, single case reports, duplicates, or reports lacking the majority of obstetrical and/or postnatal outcome data, were excluded. Any disagreement regarding inclusion of a specific article or interpretation of the data was resolved by discussion and consensus or, if required, by consulting a third author (J.D.).

We assessed the quality (good, fair and poor) and risk of bias of eligible studies using adapted criteria outlined in the Cochrane

Handbook for Systematic Reviews of Interventions and the study quality assessment tool from the American National Institutes of Health [28–30]. In cases of potential attrition (completeness of outcome data) and reporting (selective outcome reporting) bias, we contacted the corresponding authors to provide missing outcome data. When this was unsuccessful, impossible and/or the missing data were thought to introduce serious bias, we would assess the impact of including such studies in the overall assessment of results using a sensitivity analysis.

Statistical Analysis

We classified the studies based on the number of procedures completed by the team, either as early-experience or later-experience (>30 patients) studies. In order to decrease the risk of bias and perform an objective multifaceted comparison between FSBAR and OSBAR, we assessed clinical (participants, interventions and outcomes) and methodological (study design, allocation concealment, performance bias) heterogeneities between the early and later experience of FSBAR studies. In case series with raw data available, we used the D'Agostino and Pearson test to assess the distribution of continuous variables. In cases of normal distribution, data were reported as mean ± standard deviation, and unpaired Student's t test was performed to evaluate the difference between groups. Those not normally distributed were expressed as median and interquartile range and compared with the Wilcoxon test. Dichotomous variables (percentages) were compared using Fisher's exact test. p values <0.05 were considered statistically significant.

Results

Description of Studies

Our literature search identified 16 publications (fig. 1). Of these, one report published in German [31] was excluded as it was a duplicated information of 2 other reports [26, 27]. Furthermore, 3 reports were excluded on reading of the title and abstract: 1 editorial comment [32], 1 conference abstract [33] and 1 conference presentation [34]. The abstract dealt exclusively with a subset of patients requiring additional postnatal neurosurgical procedures (n = 33) [33], yet those patients were anyway included in a later report (n = 71) [35]. The selection left us with 12 eligible studies for further full-text evaluation, following which 7 reports were excluded. Two case reports from Bruner et al. [16, 18] describing the same patients (n = 4) and 1 case report from Farmer et al. [17] (n = 3) from two American teams were excluded due to incomplete data. These groups later abandoned their FSBAR program and transitioned to OSBAR because of a combination of technical failures, complications and fetal death. Two case reports and 1 case series (n = 2, 3 and 16, respectively) from Kohl et al. [19–21] were excluded because the data were incomplete and reported in a later article (n = 19) [22]. One case report from Pedreira et al. [36] was also excluded since all cases have been included in a later more complete study.

This left in total 5 case series from 2 programs for evaluation (fig. 1). From the first program (Kohl and colleagues, Germany), we included patients from 4 overlapping reports: 1 published in 2012 (n = 19), 2 in 2014 (n = 51) and 1 final report in 2015 (n = 71) [22, 26, 27, 35]. The fifth series (n = 10) came from Pedreira et al. [37] (São Paulo, Brazil).

Quality and Risk of Bias in Included Studies

Grivell et al. [38] recently demonstrated that the MOMS trial was high quality with a low risk of selection, performance, detection and other biases, yet an unclear risk of attrition and reporting bias [28, 38]. To decrease these risks, we contacted the primary investigator who provided two out of three missing variables, i.e. operation time, the number of additional postnatal procedures for the initial lesion and mean gestational age at preterm prelabor membrane rupture (PPROM). The latter data were hence included in the analysis.

From Kohl's group, the case control study by Verbeek et al. [22] (2012, n = 19) represents a good-quality report by independent assessors (table 1). However, it reports on a subset of patients evaluated at 12 months of age in the Netherlands and operated on during Kohl's early experience. They include no description of the operative, maternal, fetal, neonatal and infant outcomes. The 3 other case series (2014/2015) of the same operator are of fair or good quality with a high risk of attrition and reporting bias (table 1). The 2014 case series (n = 51) show data inconsistency concerning both gestational age at surgery and at delivery [26, 27]. Therefore, mean gestational age was recalculated according to data from the latest paper by Degenhardt et al. [26] dealing with maternal management and outcome (table 2). These 2 articles have also a high attrition bias, since the neonatal and infant outcomes are missing [26, 27]. Conversely, the most recent report (2015) on postnatal neurosurgical interventions in the first year of life (n = 71) lacks operative, maternal, fetal and neonatal outcomes (table 2) [35]. Finally, when comparing the two 2014 studies (n = 51) with the 2015 study (n = 71), which concern the same period (July 2010 to June 2013), there is a high attrition bias. Outcomes of at least 20 patients are not mentioned in the 2014 series [26, 27], and 3 patients mentioned in the 2014 studies are missing in the 2015 study, 1 who could not undergo closure and 2 who underwent double-layer closure using Surgisis® fascia patch covered by skin [35]. The data from the case series

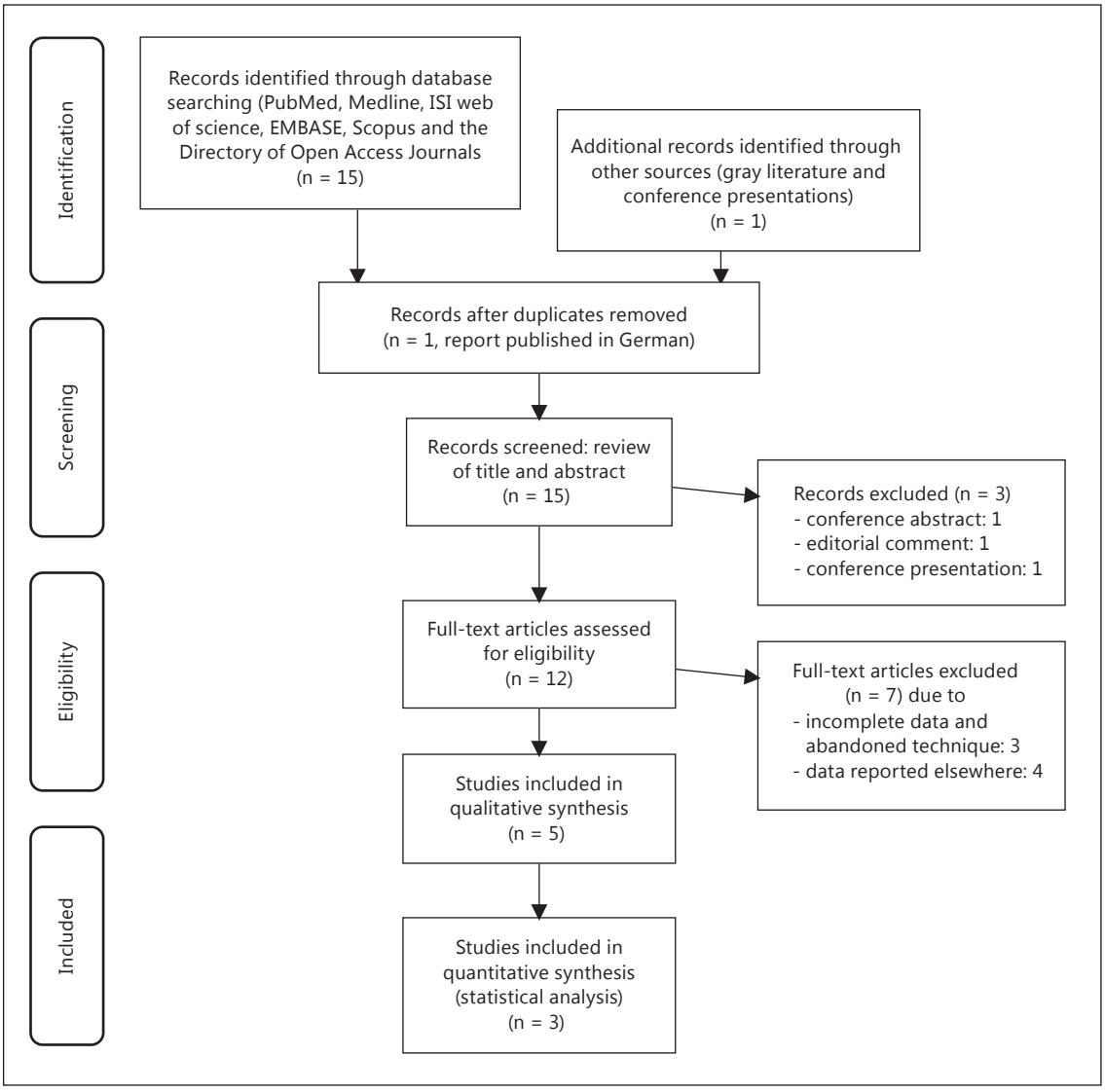

Fig. 1. Study flow diagram adapted from the PRISMA 2009 flow diagram [61].

by Pedreira et al. [37] are of good quality (table 1). Outcomes after 12 months are not available yet (table 2).

Effects of Interventions

Table 2 shows clinical and methodological heterogeneity between early and later experience with FSBAR. There is important heterogeneity in terms of subject selection. Regarding Kohl's early experience in 30 patients operated on in Bonn (Germany; 2003 to June 2010), only 19 consecutive patients (2003–2009) were eventually reported [22]. Pedreira et al. [34, 36] only operated on lumbosacral SBA patients, and the majority of patients (7/10) were operated on after 26 weeks of gestation. These differ from the criteria used in the MOMS, with the operation between 19.0 and 25.9 weeks of gestation [15]. The later-experience reports of Kohl's group have similar heterogeneity. Three consecutive papers report on patients operated on in Giessen (Germany) between July 2010 and June 2013, but do not entirely cover the same cohort. Two papers (2014) deal with the operative, maternal and fetal outcomes of 51 mothers who underwent FSBAR [26, 27], and a third paper (2015) on infant mortality and postnatal neurological outcomes at 1 year of life on 71 fetuses successfully undergoing FSBAR [35].

Table 1. Quality assessment of eligible studies using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions and the study quality assessment tool from the American National Institutes of Health (NIH) [28 – 30]

First author [Ref.], year	Scale	1	2	3	4	5	6	7	8	9	Score
Verbeek [22], 2012	NOS	1	1	0	1	1	1	1	1	n.a.	7/8
Kohl [27], 2014	NIH	1	0	0	1	1	0	0	1	1	5/9
Degenhardt [26], 2014	NIH	1	0	0	1	1	0	0	1	1	5/9
Graf [35], 2015	NIH	1	1	1	1	0	1	1	0	1	7/9
Pedreira [37], 2016	NIH	1	1	1	1	1	1	1	1	1	9/9

n.a. = Not applicable. For nonrandomized case-control studies, we used a checklist adapted from the Newcastle-Ottawa Scale (NOS) with a quality rating: quality ranked as good (6–8), fair (3–7), or poor (0–3) [30]. A study can be awarded a maximum of 1 point for each numbered item. Studies fulfilling the criteria of: (1) adequate definition of case with independent validation; (2) consecutive series of cases; (3) community controls; (4) definition of controls; (5) comparability of cases and controls; (6) ascertainment of exposure; (7) same method of ascertainment; (8) same nonresponse rate for both groups.

For nonrandomized case series, we used a checklist adapted from the NIH scale with its quality rating: quality ranked as good (7–9), fair (4–6), or poor (0–3) [29]. A study can be awarded a maximum of 1 point for each numbered item. Studies fulfilling the criteria of: (1) Was the study question or objective clearly stated? (2) Was the study population clearly and fully described, including a case definition? (3) Were the cases consecutive? (4) Were the subjects comparable? (5) Was the intervention clearly described? (6) Were the outcome measures clearly defined, valid, reliable and implemented consistently across all study participants? (7) Was the length of follow-up (≥12 months) adequate? (8) Were the statistical methods well-described? (9) Were the results well-described?

Due to the heterogeneity between fetoscopic studies reporting on early and later experience, these data could not be pooled impeding a meta-analysis for further comparison with the MOMS data. We therefore restricted our statistical analysis to the later-experience group, i.e. outcomes from the 51 patients (operative, maternal and fetal outcomes) and the 71 patients (infant mortality and postnatal neurological outcomes at 12 months) reported by Kohl's group [26, 27, 35] as compared to the 78 patients of the MOMS trial [15] (table 2).

Primary Outcome

Perinatal mortality was higher in the early experience of FSBAR. In the later experience (> 30 patients), however, perinatal mortality was comparable to the open approach (5.9 vs. 2.6%, p = 0.258; table 3).

Secondary Outcomes

Surgical Technique. In the method description, both the FSBAR [27, 36, 37] and OSBAR [15] techniques describe sharp circumferential dissection of the neural placode from the surrounding tissue, with removal of all pathological epithelial elements. However, it is unclear whether a complete untethering is performed in the fetoscopic approach, whereas for the open approach it is specified that the placode is allowed to drop into the spinal canal [15, 39]. The closure technique differs between the fetoscopic techniques from Kohl's group and from Pedreira's group. Furthermore, the fetoscopic and open approaches are technically different (table 4). OSBAR is most frequently performed in two layers (dura and skin) and without a patch. If there is insufficient dura for closure, a DuraGen® patch is used as a substitute; if it is not possible to obtain primary skin closure, relaxing incisions are made or an Alloderm® patch is used [15]. Pedreira and colleagues [40–42] describe a standardized two-layer fetoscopic closure, consisting of a subcutaneous cellulose patch which is covered by skin and acts as a scaffold for the dura, as extensively tested in animal models. The closure technique in the hands of Kohl's group evolved over time. In the early experience (≤30 cases), closure consisted of a double layer of patches (Durasis® fascia patch covered by a Gore® Preclude® Pericardial Membrane skin patch) or a single layer of Gore® Preclude® skin patch [20–22]. In the later experience on 51 FSBAR procedures, except for one incomplete closure, repair consisted of either a single layer of Surgisis® skin patch (n = 30/50, i.e. 60%), a double layer of a Surgisis® skin patch covered by a Gore® Preclude® skin patch (n = 14/50, i.e. 28%), or a triple layer of one Surgisis® skin patch covered

Table 2. Operative, maternal, fetal, neonatal and infant outcomes

	Verbeek [22], 2012	Pedreira [37], 2016	Kohl [27], 2014; Degenhardt [26], 2014	Graf [35], 2015	Adzick [15], 2011	Statistical analysis comparing later experiences	
						odds ratio (95% CI)	p value
Approach	fetoscopic	fetoscopic	fetoscopic	fetoscopic	open		
Experience	early ≤30 patients	early ≤30 patients	later >30 patients		(NOS) >30 patients		
Patients, n	19	10	51	71	78		
Operative outcomes							
Mean operation time, min	n.s.	242±89	223±40[e]	n.s.	105.2±21.8	n.a.	<0.001
Intraoperative incomplete closure	15.8% (3/19)	20% (2/10)[d]	1.9% (1/51)	n.s.	0% (0/78)	n.a.	0.395
Maternal outcomes							
Placental abruption	n.s.	10% (1/10)	0% (0/51)	n.s.	6.4% (5/78)	0 (0–1.7)	0.156
Pulmonary edema	n.s.	0% (0/10)	1.9% (1/51)	n.s.	6.4% (5/78)	0.3 (0.01–2.7)	0.402
Chorioamnionitis	23% (3/13)	0% (0/10)	5.9% (3/51)	n.s.	2.6% (2/78)	2.4 (0.3–21.2)	0.383
Oligohydramnios	62% (8/13)	40% (4/10)	13.7% (7/51)	n.s.	20.5% (16/78)	0.6 (0.2–1.8)	0.358
Chorioamniotic membrane separation	n.s.	40% (4/10)	3.9% (2/51)	n.s.	25.6% (20/78)	0.1 (0.02–0.6)	0.001
PPROM	85% (11/13)	100% (10/10)	84.3% (43/51)	n.s.	46.2% (36/78)	6.3 (2.4–16.6)	<0.001
Mean GA at PPROM, weeks	n.s.	30.2±2.7	29.7±3.1[f]	n.s.	n.s.	n.a.	n.a.
Hemorrhage requiring transfusion at delivery	n.s.	0% (0/10)	0% (0/51)	n.s.	9% (7/78)	0 (0–1.2)	0.042
Uterine thinning or dehiscence	n.s.	0% (0/10)	0% (0/51)	n.s.	35.5% (27/76)	0 (0–0.2)	<0.001
Fetal, neonatal and infant outcomes[a]							
Mean GA at birth, weeks	n.s. (median, 32)	32.4±1.9	32.9±2.7[f]	32.3, n.s. (24.4–38.3)[g]	34.1±3.1	n.a.	0.03
Preterm birth <30 weeks	n.s.	11.1% (1/9)	11.8% (6/51)	12.7% (9/71)	12.8% (10/78)	0.99 (0.3–2.8)	1.000
Respiratory distress syndrome	92.3% (12/13)	0% (0/9)	n.s.	n.s.	20.8% (16/77)	n.a.	n.a.
Postnatal additional SBA recoverage[b]	n.s.	28.6% (2/7)	n.s.	23.9% (17/71)	2.6% (2/77)	14.9 (3.1–96.6)	<0.001
Complete reversal of CM at 1 year	n.s.	85.7% (6/7)	n.s.	n.s.	35.7% (25/70)	n.a.	n.a.
Shunt rate at 1 year	30.8% (4/13)	42.8% (3/7)	n.s.	45% (32/71)	40.3% (31/77)	1.2 (0.6–2.5)	0.619
Surgery for tethered cord at 1 year	n.s.	0% (0/7)	n.s.	4.2% (3/71)	7.8% (6/77)	0.5 (0.1–2.5)	0.497
CM decompression surgery at 1 year[c]	n.s.	0% (0/7)	n.s.	4.2% (3/71)	1.3% (1/77)	3.4 (0.3–85.7)	0.350
Ability to walk independently at 2.5 years	n.s.	n.s.	n.s.	n.s.	41.9% (26/62)	n.a.	n.a.

Statistical comparison of outcomes in later-experience series on the right. n.a. = Not applicable; n.s. = not specified; GA = gestational age; US = ultrasound; MRI = magnetic resonance imaging.

[a] Based on the number of live born infants. [b] Postnatal reoperation in case of dehiscence of all layers. For clarity, partial dehiscence not requiring reoperation was reported in 13% of cases (10/77) for open repair; for FSBAR it was not mentioned. [c] Degree of CM is a mandatory inclusion criterion for fetal surgery, whatever the approach. It is assessed pre- and postnatally by US and/or MRI. [d] Surgery could not be completed in 2 cases due to trocar dislodgment and CO2 leakage to the maternal abdomen. [e] Normal distribution with exclusion of 1 case where the operation was abandoned. [f] Data from both reports are discrepant; results displayed are based on the last paper [26]. [g] Range.

by two Gore® Preclude® skin patches (n = 2/50, i.e. 4%), a double layer of Surgisis fascia patch covered by skin (n = 2/50, i.e. 4%) or a single layer of normal skin (2/50, i.e. 4%) [26, 27]. Finally, in the latest study on 71 FSBAR, closure consisted of a single layer of Surgisis® skin patch (48/71, i.e. 67.6% of cases), a double or triple layer of one Surgisis® skin patch covered by 1–2 Gore® Preclude® skin patches (21/71, i.e. 29.6%) or a single layer of normal skin (2/71, i.e. 2.8%) [35]. In summary, the German group in its 3 last publications described a single-layer Surgisis® patch-augmented closure of the skin after undermining the lesion as the most commonly performed technique in 30/50 (60%) [26, 27] and 48/71 (67.6%) patients [35] (table 4). From the above, it should be clear that FSBAR would actually be more accurately described as fetoscopic patch coverage of SBA.

Operative Outcomes. In both the early experience of Pedreira and Kohl and the later experience of Kohl, FSBAR required double the operation time than the reference OSBAR (223 ± 40 vs. 105.2 ± 21.8 min, p < 0.001). The rate of incomplete closure was as high as 15.8–20% in the early experience. However, with a greater caseload,

Table 3. Mortality rate for FSBAR with statistical analysis for comparison of later-experience fetoscopic studies to OSBAR

	Verbeek [22], 2012	Pedreira [37], 2016	Kohl [27], 2014; Degenhardt [26], 2014	Graf [35], 2015	Adzick [15], 2011	Statistical analysis comparing later experience	
						odds ratio (95% CI)	p value
Approach	fetoscopic	fetoscopic	fetoscopic	fetoscopic	open		
Surgical experience	early ≤30 patients	early ≤30 patients	later >30 patients				
Total number of patients included	19	10	51	71	78		
Death within 7 postoperative days	10.5% (2/19)[a] 2 IUFD	10% (1/10) 1 IUFD	1.9% (1/51) 1 NND	n.s.	2.6% (2/78) 1 IUFD, 1 NND	0.760 (0.027–11.105)	1.000
Perinatal mortality	15.8% (3/19)	20% (2/10)	7.8% (4/51)[b]	n.s.	2.6% (2/78)	3.234 (0.482–26.604)	0.212
Infant mortality	5.9% (1/17)	11.1% (1/9)	n.s.	7% (5/71)[c]	1.3% 1/77)	5.758 (0.628–133.645)	0.105

n.s. = Not specified; IUFD = in utero fetal demise; NND = neonatal death. [a] One pregnancy underwent termination because FSBAR was complicated by placental bleeding after trocar removal due to trocar injury to anterior placenta; another died in utero immediately after the end of the procedure. [b] One death after preterm delivery due to chorioamnionitis at 24.6 weeks, about 1 week after the procedure. During the first months of life, 2 infants died due to persisting CM. One last child died of trisomy 13 after delivery at 36 weeks. [c] Five children died in the 1st year of life due to complications of a persisting CM (2/71), prematurity (2/71) and trisomy 13 (1/71).

Table 4. Comparison of surgical techniques

	Verbeek [22], 2012	Pedreira [37], 2016	Kohl [27], 2014; Degenhardt [26], 2014	Graf [35], 2015	Adzick [15], 2011
Patients, n	19	10	51	71	78
Approach	fetoscopic	fetoscopic	fetoscopic	fetoscopic	open
Experience	early ≤30 patients	early ≤30 patients	later >30 patients		
Placode dissection with untethering	n.s.	n.s.	n.s.	n.s.	complete
Dural closure	none	none	none	none	primary running suture (DuraGen® patch when necessary)
Musculofascial closure	Durasis® patch	cellulose patch	(exceptionally in 2 cases, Surgisis® patch)	none	running suture
Skin closure	Gore® Preclude® patch	running suture	Surgisis® ± Gore® Preclude® patch	Surgisis® ± Gore® Preclude® patch	running suture (Alloderm® when necessary)

n.s. = Not specified.

incomplete closure of the defect was as frequent in FSBAR as in OSBAR (1.9 vs. 0%, p = 0.395; table 2).

Maternal and Fetal Outcomes. In the early experience of FSBAR, the rates of chorioamnionitis, oligohydramnios, PPROM, prematurity, additional postnatal surgical procedures and respiratory distress syndrome were higher compared to MOMS data. Shunt rate at 1 year was comparable (30.8–42.8 vs. 40.1%). Due to incomplete data, no other conclusion could be drawn on the following outcomes: operation time, placental abruption, pulmonary edema, chorioamniotic membrane separation, mean gestational age at PPROM, hemorrhage requiring transfusion at delivery, uterine thinning or dehiscence, postnatal additional SBA recoverage, complete reversal of CM at 1 year, surgery for tethered cord at 1 year and ability to walk independently at 2.5 years (table 2).

In the later experience, FSBAR was associated with double the PPROM rate (84 vs. 46%, p < 0.001), an earlier gestational age at birth (32.9 vs. 34.1 weeks, p = 0.03) and a 10 times higher need for additional postnatal SBA

surgery (28 vs. 2.56%, $p < 0.001$). There was no difference in the rate of oligohydramnios, pulmonary edema, placental abruption and chorioamnionitis, neither was there a difference in need for shunting, untethering of the cord or CM decompression at 12 months. FSBAR was associated with a lower rate of hemorrhage requiring transfusion at delivery (0 vs. 9%, $p = 0.042$), a 6 times lower rate of chorioamniotic membrane separation (4 vs. 26%, $p = 0.001$) and a complete absence of scar thinning or uterine dehiscence (0 vs. 36%, $p < 0.001$). Given the absence of certain postnatal outcomes for FSBAR (respiratory distress syndrome, complete reversal of CM at 1 year and ability to walk independently at 2.5 years), no comparison could be made for those parameters (table 2).

Discussion

The objective of our systematic review was to compare operative techniques and outcomes of FSBAR with OSBAR. We conclude that after 30 cases FSBAR (1) is technically different from OSBAR; (2) has comparable perinatal mortality, intraoperative incomplete closure rate, placental abruption rate, pulmonary edema rate, chorioamnionitis rate, oligohydramnios rate, shunt or untethering of the cord or CM decompression rate at 12 months; (3) has a longer operation time, double the PPROM rate, earlier gestational age at birth, a 10 times higher need for additional postnatal SBA surgery; (4) has a 6 times lower rate of chorioamniotic membrane separation and absence of hemorrhage requiring transfusion at delivery and of uterine thinning or dehiscence. Neonatal outcomes, complete reversal of CM at 1 year and neurological functional outcomes at 2.5 years for FSBAR are not yet available; hence, no comparison can be made.

When compiling the data on FSBAR, we discriminated between the early and later operator experiences as those describing the early experience and those on later experience. Even if no learning curve has been objectively assigned yet, we used a cutoff of 30 cases, as suggested by Kohl et al. [27], a number that is also quoted for other fetoscopic surgeries, such as laser [43], or for complex laparoscopic procedures [44–47]. In fact, perinatal mortality, intraoperative incomplete closure rate and shunt rate at 12 months was comparable to OSBAR after 30 cases. For both the early and late experiences, a significant risk for inconsistency and attrition bias was observed. For the early experience, there is only 1 report on 13/19 patients who were neurologically evaluated at 1 year by an independent assessor, yet comparable outcomes on the other patients operated on during the same time period were to our knowledge not published [22]. Therefore, only the study from Brazil provides a complete data set on early experience [37]. For the later experience, a discrepancy of at least 20 patients was observed in subsequent reports from Kohl's group [26, 27, 35], though they cover the same time period.

We observed that both fetoscopic and open approaches yield comparable short-term neuroprotection, despite quite large differences in the operative technique. This is remarkable and often goes unnoticed. Whereas the majority of open procedures are done in a very similar manner to what is done during a postnatal procedure, i.e. dissection of the neural placode and closure of the defect in two or three layers, the description of FSBAR is less clear regarding the extent of spinal cord untethering. FSBAR also systematically substitutes the layered closure by patch-augmented repair of dura and/or skin. During OSBAR, the use of patch augmentation is limited to patients with insufficient dura for closure and/or when it is not possible to obtain skin closure [15]. Remarkably, this difference in the technique does not seem to impact some short-term neurological outcomes, as evidenced by comparable numbers of procedures for CM decompression and shunting. To our knowledge, the efficacy of patch augmentation of the German technique has not been formally compared with a standard multilayered repair in an experimental setting [27, 48]. If the water tightness of the repair would be considered as an essential part of the operation, it would be good to experimentally prove this for any alternative technique. This should not exempt procedures relying on a patch for watertight closure. The German pioneers of FSBAR acknowledge the importance of this aspect and propose the 'bulging patch' water tightness test at the end of the procedure; yet, to our knowledge, that test has not yet been validated [27].

As a consequence of the difference in the technique, incomplete closure of the defect did not occur prenatally after OSBAR as opposed to FSBAR. Despite that, the intraoperative incomplete closure rate was not significantly higher after FSBAR. The latter also leads to a higher need for additional postnatal procedures at the level of the lesion. In an initial conference abstract on their later experience, the German group reported a postnatal recoverage rate of up to 40% (n = 33) [33]. In the last case series, reoperation was required in 24% because of cerebral spinal fluid leakage (41%), incomplete closure (29.5%), or a skin defect (29.5%) [35]. Initially often (15.8–20%), yet later very rarely (1.9%), the in utero procedure had to be abandoned prematurely, leaving the neurosurgical repair

incomplete. The reasons may be maternal factors such as obesity, but also other technical limitations such as the size of the defect, suboptimal fetal position and an anterior placenta precluding appropriate port insertion [33, 35]. This points to the challenge of performing an in utero endoscopic repair with the currently available technology.

Another clinically relevant parameter is the need for postnatal untethering after complete in utero SBAR. In postnatally repaired SBA patients, tethered cord syndrome occurs in 78–100% of cases. It is usually a secondary effect of scar tissue formation at the surgical site, and about 20–50% of children will eventually require surgical untethering [11, 13, 49]. Whether prenatal OSBAR increases the need for untethering has always been a matter of debate, but in the MOMS trial it was not recognized in the medium term [15]. In this review, surgery for tethered cord at 1 year after FSBAR was comparable to that of OSBAR.

There is a striking effect of increasing experience resulting in a decrease in side effects. Early FSBAR experience [22, 37] was associated with higher mortality rates, oligohydramnios, PPROM and prematurity when compared to later OSBAR experience (table 2). The reason for the persistently high PPROM rates remains unclear. It seems tempting to relate that to the need for multiple trocars, as previously observed for multiple port cord occlusion [27, 36, 50–53]. Also the size of the puncture sites may play a role. Ports have an outside diameter of either 4 (12 Fr), 5 or 5.3 (16 Fr) mm, yet their membrane defects after delivery range from 20 to 100 mm in diameter [36]. This has been previously observed for single puncture procedures as well [54]. Other factors might play a role: the use of CO_2 insufflation, the lengthy procedure and the percutaneous approach. The latter locks at least 3 trocars in the uterus and invites significant shearing forces to the uterus and the amniotic membranes when the instruments are manipulated in any but the axial direction. Whether this problem will be solved either by better closure techniques [27, 36, 55] or reducing the number of trocars will need to be demonstrated. Meanwhile, PPROM – hence prematurity – remains the 'Achilles's heel' of fetoscopic surgery [56]. Anyway, all the above technical differences as well as the different outcomes for each specific parameter should prompt caution when comparing outcomes.

There is one very relevant benefit from FSBAR, which cannot be ignored. From a maternal viewpoint, apart from a lesser invasiveness at the time of the procedure, no thinning or dehiscence at the level of the port insertions was observed at the time of delivery. This could mean that the uterus is less compromised in the index as well as in future pregnancies, potentially shortening the interval between pregnancies. However, determinations of uterine thinning or dehiscence were subjective and not defined a priori in any of the techniques. In the absence of complications, the delivery mode has been by a cesarean section at 37 weeks following OSBAR (lower uterine segment) versus 39 weeks after FSBAR (no description). No clinical relevance has yet been assigned to this uterine finding, with no future childbearing recommendations published beyond the cesarean section for open fetal surgery. Mothers are currently advised to delay conception for 18–24 months and in subsequent pregnancies to deliver at 36 weeks by the cesarean section before the onset of labor [57]. Long-term follow-up has shown no difference in subsequent maternal fertility [57, 58].

There are several limitations to our systematic review. This is primarily because of potential analytical bias in the review process. Firstly, this review eventually concerns only 3 reports from one German group with sufficient experience with FSBAR. Secondly, the inclusion criteria for fetal surgery vary between groups, although CM is mandatory regardless of the approach. In the MOMS trial, repair was limited between 19 and 26 weeks because efficacy of later procedures was not demonstrated [59, 60]. For FSBAR, the Brazilian team operated between 25 and 28 weeks, with 70% of patients being operated after 26 weeks [34, 36]. If it is correct that the effects of a later operation are minimal or absent, the above-reported outcomes from the Brazilian group are actually an underestimation of effect. The German team performed the operations up to 29 weeks' gestation, yet the vast majority (67/71 patients) were operated on prior to 26 weeks [26, 27, 35]. Therefore, we assume that the currently observed effect is representative of what can be expected. Finally, when comparing the need for a shunt, a cautious conclusion should be drawn as the numerous criteria for shunt placement differ between all FSBAR and OSBAR institutions.

In conclusion, multitrocar FSBAR is technically different from its open alternative. Accepting the many limitations for an appropriate comparison, we conclude that, following an initial learning curve, FSBAR increases the risk for PPROM and premature delivery. Moreover, the operative time is much longer than with open repair, but the clinical consequences of that finding are not yet clear, whereby the fetus remains in a warm and liquid environment. FSBAR definitely reduces maternal morbidity and avoids uterine scar problems inherent to hysterotomy.

Perioperative mortality is comparable, as well as outcomes at 12 months, except for complete reversal of CM that is not reported. Long-term outcomes will be required, both to evaluate spinal as well as brain function. In the absence of convincing data, we can expect continuing controversy on whether both procedures are equally effective. Ideally, a head-to-head comparison of both approaches would be required in an appropriately sized randomized controlled trial. Given the multicentric experience with both procedures, this represents a tremendous challenge, unless an alternative design is agreed on. Prospective data collection in a dedicated international registry could offer a valid alternative to compare the different approaches. Meanwhile, it seems cautious to consider FSBAR an investigational procedure. It seems also cautious to insist on further translational research, particularly to investigate whether patch repairs are as effective as layered repairs. Furthermore, a rigorous translational investment in the technical progress may make fetoscopic repair more effective and less traumatic to the membranes.

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